REMARKS

Applicants respectfully request entry of the above amendments and reconsideration of the following arguments pursuant to 37 C.F.R. § 1.111.

1. Restriction Requirement

Applicants appreciate the Office's withdrawal of Restriction Requirement mailed March 5, 2009, and rejoinder of all the claims.

2. Status of the Claims

Claims 1-14 stand pending and rejected.

Upon entry of the present amendments, Applicants amend claim 2 to more precisely recite the claimed subject. Support for the amendment can be found, for example, in claim 1 as originally filed. Applicants do not believe that the amendments add prohibited subject matter that is unsupported in the Specification as filed.

3. Acknowledgement of the Drawings

Applicants appreciate the Office's acknowledgement that the drawings submitted September 15, 2006, are deemed acceptable.

4. Acknowledgement of Priority

In the Office Action Summary, the Office indicates that none of the certified copies of the priority documents have been received.

Applicants attach a copy of the PCT/IB/304 form which indicates that a copy of the priority document was transmitted to the designated offices (*see* enclosed **Exhibit 1**). Thus, the U.S. Patent and Trademark Office should be in possession of the certified priority document. Please see M.P.E.P. § 1893.03(c) and PCT Rule 17, to which Applicants have complied.

5. Acknowledgement of Information Disclosure Statements

Applicants appreciate the Office's acknowledgement of the Information Disclosure Statement (IDS) filed September 15, 2006.

6. Rejection of the Claims under 35 U.S.C. § 103(a)

The Office rejects claims 1-14 under 35 U.S.C. § 103(a) as allegedly obvious over **WO 03/000698** ("the '698 publication").

6.1 Claims 1-2, 7-8, and 10

The Office lists eleven (11) compounds described in the '698 publication. Office Action, pages 3-6. The Office argues that some of the listed compounds allegedly fall within the genus recited in present claim 1, except for the radioactive labeling on the benzoyl group. *Id.*, at 3. Relying on the teachings on p. 13 and Scheme 2 of the '698 publication, the Office alleges, "the '698 publication teaches compounds which meet the limitations of generic claim 1 and further suggests that certain of these compounds are suitable for radiolabeling, thereby rendering claims 1, 2, 7, 8, and 10 obvious." *Id.*, at 6.

Applicants traverse. Structural similarity between compounds is not by itself sufficient to establish obviousness, ***unless*** "the prior art gives reason or motivation to make the claimed compositions." *See In re Dillon*, 919 F.2d 688, 692, 16 U.S.P.Q.2d 1897, 1901 (en banc) (Fed. Cir. 1990); *Takeda Chem. Indus. Ltd. v. Alphapharm Pty. Ltd.*, 492 F.3d 1350, 1356, 83 U.S.P.Q.2d 1169, 1174 (Fed. Cir. 2007).

Among the eleven (11) compounds listed, the Office is respectfully reminded that the compounds of claim 1 differ from compounds 1), 2), and 4) in the following manner. First, the claimed compounds have a radiolabeled substituent. None of compounds 1), 2), and 4) encompasses a radiolabel atom. Second, the radiolabeled substituent of the claimed compounds are at the 4-position (para-position) of the benzoyl group. The substituent(s) of compounds 1), 2), and 4) of the '698 publication are at 2-, 3-, and 3, 4-position(s), respectively, and are *not radiolabeled.* Thus, the '698 publication fails to teach all the recited elements presently claimed.

Additionally, there is no suggestion to add a radiolabeled group to the 4-position in particular, over any other position, let alone an expectation that such a modification would have had an expectation of success. The Office is directed to the paragraph bridging pages 9-10 of the Specification:

> TBOA occurs as four stereoisomers and the (2S,3S) compound shows the strongest activity among them. The substituent on the benzoyl ring may be located at three positions, i.e., ortho-, meta- and para-positions. ***Studies on the structure-activity-relationship of these compounds clarified that the para-compound shows the strongest activity.*** Therefore, in the following synthesis scheme the introduction of a radioactive substituent is shown by taking compounds having a (2S,3S)-configuration in the aspartic acid and having the substituent at the para-position on the benzoyl, though all isomers having different substitution or configuration manners are included in the scope of the present invention.

(emphasis added). There was no indication, absent testing, that substitution at one position over another had any different activity. Thus, there may have been at most an invitation to experiment, but that is all. The finding is unexpected.

In fact, the '698 publication describes that strongest activity results from the ***meta-position*** of the amino group on the benzene ring, ***not*** the para-position. *See* page 8, lines 7-17 of the '698 publication. A skilled artisan, in view of the '698 publication would not have been directed to even try to modify the para-position. Thus, the '698 publication also fails to render the claims "obvious to try." The Office also fails to provide any evidence showing there is guidance in the art to make and/or use the claimed compounds.

Scheme 2 of the '698 publication teaches preparing radio-labeled methoxy-substituent. The Office is reminded that claim 1 does not recite a radio-labeled methoxy-substituent. Instead, claim 1 recites, *inter alia*, the following radio-labeled substituents:

1) a straight or branched lower aliphatic alkyl group;

2) a hydroxyl group;

3) a straight or branched lower aliphatic alkoxy group;

4) an amino group;

5) a straight or branched lower aliphatic acylamido group;

6) a halogen atom; and

7) a straight or branched lower aliphatic haloalkyl group.

The '698 publication does not provide any "reason or motivation" to make the claimed radio-labeled substitute. Accordingly, the alleged structural similarity is not by itself sufficient to establish obviousness. *See Dillon*, 919 F.2d at 692, 16 U.S.P.Q.2d at 1901; *Takeda*, 492 F.3d at 1356, 83 U.S.P.Q.2d at 1174.

Furthermore, the presently claimed compounds and methods offer unexpected advantages. Scheme 2 of the '698 publication teaches preparing radio-labeled methoxy-substituent. The present claims recite, *inter alia*, labeling with ^{125}I (*e.g.*, claim 2). The labeling with ^{125}I offers at least the following advantages:

1) ^{125}I emits a gamma ray, which enables direct detection with brain imaging;

2) ^{125}I can be detected noninvasively in SPECT (single photon emission computed tomography); and

3) the binding activity of iodide-substitute (IC_{50} = 4.8 nM) is higher than the methoxy-substituent (IC_{50} = 12 nM).[1]

Additionally, the present claims recite, *inter alia*, labeling with tritium gas (*e.g.*, claims 2, 10 and 13-14). The tritium gas labeling process is capable of producing purer products with a higher yield, compared to the methylation of a phenoric hydroxyl group as shown in Scheme 2 of the '698 publication. *See* right column under "Material and Methods," page 295, Shimamoto et al., 71 MOL. PHARMACOL. 294 (2007) ("Shimamoto") (enclosed as **Exhibit II**). The resultant tritium-containing ethyl-substitute offers the highest binding activity (IC_{50} = 3.2 nM). *See* Specification, Table 2, page 25. Tritium gas labeling enables the development of a "binding assay," which is superior to the conventional "uptake assay." *See* Shimamoto., right column under "Discussion" on page 299 to page 301.

Thus, the '698 publication fails to render claims 1-2, 7-8, and 10 obvious. The rejection should be withdrawn, and the claims allowed.

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[1] *See* Specification, Table 2, page 25; the '698 publication, Table 1, page 37. The IC_{50} was determined as the ability to inhibit the uptake of [^{14}C]-glutamic acid by human EAAT2 and EAAT3 stably expressed in MDCK (Madin-Darby canine kidney) cells or transiently expressed in COS-1 cells. *See* Specification, paragraph bridging pages 24-25.

6.2. Claim 9

The Office asserts that claim 9 is purportedly obvious over the '698 publication, because the '698 publication allegedly teaches that the radiolabeled ligands are useful for identification of glutamate transporter proteins. Office Action, pages 6-7.

Applicants traverse. Claim 9 depends indirectly from claim 1. Claim 1 is nonobvious for the reasons discussed in Section 6.1 *supra*. Therefore, claim 9 is similarly nonobvious. Additionally, there is no teaching that would have led a skilled artisan to have identified and used the claimed compounds to identify or characterize glutamate transporter proteins.

In view of the above arguments, claim 9 is nonobvious over cited art. The rejection should be withdrawn and the claim allowed.

6.3. Claims 5-6 and 13-14

Claims 5-6 and 13-14 stand rejected because schemes 1-2 of the '698 publication allegedly depict the process of the claims.

Applicants traverse. Claims 5-6 and 13-14 depend directly or indirectly from claim 1. Claim 1 is nonobvious for the reasons argued in Section 6.1 *supra*. Additionally, the Office mischaracterizes the claimed precursors or methods in claims 5-6 and 13-14. The claimed processes differ from the process described in Schemes 1-2 of the '698 publication. Scheme 1 of the '698 publication does not describe the production of the claimed benzoylamido substituent. Scheme 2 of the '698 publication describes the production of radiolabeled substituent through the hydroxybenzoyl intermediate. *See* page 13, lines 7-8 of the '698 publication. The methods of claims 5-6 and 13-14 do not use such a hydroxybenzoyl intermediate. Therefore, the '698 publication fails to suggest all the elements of claims 5-6 and 13-14.

Thus, the Office has failed to adduce a *prima facie* obviousness rejection to claims 5-6 and 13-14. Applicants respectfully request withdrawal of the rejection and allowance of the claims.

6.4. Claims 3-4 and 11-12

The Office apparently also rejects claims 3-4 and 11-12 without providing any reasoning when it concludes "Schemes 1 and 2 also render obvious Applicant's precursor compounds recited in claims 3, 4, 11, and 12." Office Action, page 7.

Applicants traverse. Claims 3-4 depend directly or indirectly from claim 1. Claim 1 is nonobvious over the art for the reasons discussed in Section 6.1. Claims 3-4 stand nonobvious additionally for the reasons argued in Section 6.3. Accordingly, the rejection as to claims 3-4 should be withdrawn and the claims allowed.

Turning to claims 11-12, these claims depend indirectly from claim 1. Claim 1 fails to be obvious for the reasons asserted in Section 6.1 *supra.* Scheme 1 of the '698 publication does not describe the production of the claimed benzoylamido substituent. Second, Scheme 2 of the '698 publication describes the production of radiolabeled substituent through the hydroxybenzoyl intermediate. *See* page 13, lines 7-8 of the '698 publication. The methods of claims 11-12, however, do not use such a hydroxybenzoyl intermediate. Thus, the '698 publication fails to suggest all the limitations of claims 11-12. The rejection as to claims 11-12 should be withdrawn and the claims allowed.

In summary, claims 1-14 are nonobvious over the '698 publication. Applicants respectfully request withdrawal of the rejection and allowance of the claims.

7. Double Patenting Rejection

The Office rejects claims 1-14 additionally on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 6-7, 10, 12, and 14-15 of **U.S. Patent No. 7,247,652** ("the '652 patent"). The Office admits that the presently claimed compounds differ from those recited in the claims 6-7 of the '652 patent at the atom(s) or group(s) at the R^1 and R^2 positions. Office Action, page 8. The Office further admits that the claimed compounds allegedly have lower aliphatic alkyl groups, while the compounds in the claims 6-7 of the '652 have hydrogen atoms. *Id.* However, the Office asserts that "substitution of methyl for hydrogen is obvious in cases where the compounds would be expected to confer similar properties." *Id.* The Office then concludes that the substitution of the hydrogen atom for

the methyl group would have been purportedly obvious, because such a substitution allegedly does not affect the glutamate uptake inhibitory activity. *Id.*

Applicants traverse. The nonstatutory obviousness-type double patenting rejection, if not based on an anticipation rationale, is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103" except that the patent principally underlying the rejection is not considered prior art. *See* M.P.E.P. § 804 (quoting *In re Braithwaite*, 379 F.2d 594, 600 n.4, 154 U.S.P.Q. 29, 34 (C.C.P.A. 1967)).

Claims 6-7, 10, and 12 of the '652 patent fail to suggest the substituent position in the benzoyl group, while the present claims recite a substituent at the para-position (4-position) of the benzoyl group. The Office is directed to the paragraph bridging pages 9-10 of the Specification:

> TBOA occurs as four stereoisomers and the (2S,3S) compound shows the strongest activity among them. The substituent on the benzoyl ring may be located at three positions, i.e., ortho-, meta- and para-positions. ***Studies on the structure-activity-relationship of these compounds clarified that the para-compound shows the strongest activity.*** Therefore, in the following synthesis scheme the introduction of a radioactive substituent is shown by taking compounds having a (2S,3S)-configuration in the aspartic acid and having the substituent at the para-position on the benzoyl, though all isomers having different substitution or configuration manners are included in the scope of the present invention.

(emphasis added). Such a finding is unexpected. At best, it could have been construed as invitation to experiment with the different positions, but an invitation to experiment does not render the claims obvious. The activity of the compounds substituted at the para-position is further unexpected. The '652 patent describes that strongest activity results from the ***meta-position*** of the amino group on the benzene ring, ***not*** a substitution at the para-position, let alone what should have been substituted at the para-position to obtain that result. *See* col. 4, lines 51-62 of the '652 patent. A skilled artisan, in view of the '652 patent, but unaware of the present disclosure, would not have led to make a compound having a substituent at the para-position, let alone radiolabeling it. Additionally, there would have been no expectation that such a compound would have worked.

Furthermore, claims 14-15 of the '652 patent recite a method for inhibiting a L-glutamate transporter or L-glutamate uptake by ***administering*** the compound. The present claims do not

recite such a use. Instead, present claim 9 recites using the radiolabeled compound to ***examine not to inhibit*** distribution and/or expression of glutamate transporter and/or glutamate uptake level in a biological sample. The present claims thus differ from claims 14-15 of the '652 patent. The present Specification further distinguishes by stating:

> ***By radio-labeling such a selective and high-affinity ligand of the transporter, a specific binding even in a trace amount could be detected.*** Thus, such radio-labeling would bringing about a significant contribution in the filed of drug searching ***based on binding experiments to screen for novel ligands and isolate novel proteins***. It would also be expected that the distribution and expression of the glutamate transporter and the level of its ability to take up glutamate could be visualized with the use of autoradiography and positoron emission tomography (PET) techniques. However, no compound usable in the detection of specific bindings or the visualizing techniques has been known from the view point of satisfactory affinity and selectivity.

See lines 6-18, page 5 of the Specification (emphasis added). Without teaching all elements of claims 9, let alone claims 14-15, these claims are nonobvious over the '652 patent.

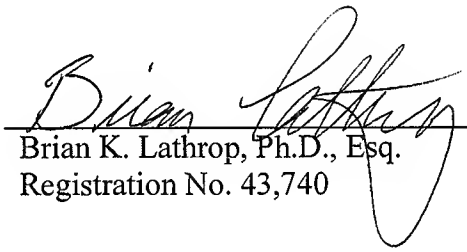
In view of the above arguments, claims 1-14 are nonobvious over claims 6-7, 10, 12, and 14-15 of the '652 patent. Applicants respectfully request withdrawal of the rejection and allowance of the claims.

CONCLUSION

Should the Office have any questions or comments regarding Applicants' amendments or response, please contact Applicants' undersigned representative. Furthermore, please direct all correspondence to the below-listed address.

In the event that the Office believes that there are fees outstanding in the above-referenced matter and for purposes of maintaining pendency of the application, the Office is authorized to charge the outstanding fees to Deposit Account No. 50-0573. The Office is likewise authorized to credit any overpayment to the same Deposit Account Number.

Respectfully Submitted,

Date: May 24, 2010 By: 

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